**Citation:**

Yamagishi K, Iso H, Date C, Fukui M, Wakai K, Kikuchi S, Inaba Y, Tanabe N, Tamakoshi A; Japan Collaborative Cohort Study for Evaluation of Cancer Risk Study Group. Fish, omega-3 polyunsaturated fatty acids, and mortality from cardiovascular diseases in a nationwide community-based cohort of Japanese men and women. The JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) Study. *J Am Coll Cardiol.* 2008 Sep 16;52(12):988-96.

**PubMed ID:** 18786479

**Study Design:**

Prospective Cohort Study

**Class:**

B - Click here for explanation of classification scheme.

**Research Design and Implementation Rating:**

POSITIVE: See Research Design and Implementation Criteria Checklist below.

**Research Purpose:**

To test the hypothesis that fish or omega-3 polyunsaturated fatty acids intakes would be inversely associated with risks of mortality from ischemic heart disease, cardiac arrest, heart failure, stroke and total cardiovascular disease.

**Inclusion Criteria:**

- Men and women subjects from the JACC
- Aged 40 - 79 years during the baseline period (1988 - 1990)

**Exclusion Criteria:**

- Persons who reported a history of heart disease (IHD, arrhythmia, heart failure, or unspecified heart disease), stroke, or cancer at the baseline survey
- Those missing the fresh fish item, with more than 1 item missing from the other 3 fish items, or with more than 4 missing items from the 33 items on the dietary questionnaire

**Description of Study Protocol:**

**Recruitment**

- Subjects from the JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) study, a nationwide, community-based follow-up study of cardiovascular disease with one of the largest number of subjects in Asia (110,792 persons) from 45 administrative districts of Japan

**Design:** Prospective cohort study

**Blinding used (if applicable):** not applicable

**Intervention (if applicable):** not applicable

**Statistical Analysis**

- Age-adjusted means and proportions of cardiovascular risk factors and nutrients were calculated according to quintiles of energy-adjusted dietary intakes of fish and omega-3 PUFA and the overall difference across the quintiles was tested by ANCOVA
- Hazard ratios and 95% confidence intervals were calculated according to quintiles of fish or omega-3 PUFA intake after adjustment for age, gender, BMI, history of hypertension and diabetes mellitus, smoking status, alcohol intake, perceived mental stress, walking, sports, education levels, and continuous values of total energy and energy-adjusted nutrient and vegetable and fruit intakes

**Data Collection Summary:**

**Timing of Measurements**

- At baseline, participants completed self-administered questionnaires concerning their lifestyle and medical histories of previous cardiovascular disease or cancer
- Participants were followed for 12.7 years

**Dependent Variables**

- Mortality from cardiovascular diseases (stroke, subarachnoid hemorrhage, intraparenchymal hemorrhage, ischemic stroke, IHD, myocardial infarction, cardiac arrest, arrhythmic death, heart failure, total cardiovascular disease)
- Investigators conducted a systematic review of death certificates

**Independent Variables**

- Dietary intakes of fish and omega-3 PUFA were determined by food frequency questionnaire
- Food frequency questionnaire contained 33 foods, including 4 fish items (fresh fish, steamed fish paste, dried or salted fish, and deep-fried fish), with five choices presented for each item (rarely, 1 to 2 days per month, 1 to 2 days per week, 3 to 4 days per week, and almost every day)

**Control Variables**

- Age
- Gender
- BMI
- History of hypertension and diabetes mellitus
- Smoking status
- Alcohol intake
- Perceived mental stress
- Walking
- Sports
- Education levels
- Continuous values of total energy and energy-adjusted nutrient and vegetable and fruit

intakes

**Description of Actual Data Sample:**

**Initial N**: Original cohort had 110,792 persons (46,465 men and 64,327 women)

**Attrition (final N):** 57,972 persons (22,881 men and 35,091 women) had complete dietary info

**Age**: Participants were 40 to 79 years of age during baseline period (1988 - 1990)

**Ethnicity**: assumed Asian

**Other relevant demographics**:

**Anthropometrics**

**Location**: Japan

**Summary of Results:**

**Key Findings**

- Quintiles of energy-adjusted fish intake were 0 - 27, 27 - 39, 39 - 53, 53 - 72, and 72 - 229 g/day
- Quintiles of omega-3 PUFA intake were 0.05 - 1.18, 1.18 - 1.47, 1.47 - 1.75, 1.75 - 2.11, and 2.11 - 5.06 g/day
- During 735,905 person-years of follow-up for 57,972 persons, there were 419 deaths due to IHD (including 329 myocardial infarctions), 107 due to cardiac arrest, 307 due to heart failure, and 972 due to stroke (including 223 intraparenchymal hemorrhages, 153 subarachnoid hemorrhages, and 319 ischemic strokes); there were 2,045 total cardiovascular deaths and 7,008 total deaths
- There were generally inverse associations of fish and omega-3 PUFA intakes with risks of mortality from heart failure (multivariable hazard ratio for highest versus lowest quintiles = 0.76 [95% confidence interval: 0.53 to 1.09] for fish and 0.58 [95% confidence interval: 0.36 to 0.93] for omega-3 PUFA).
- Associations with ischemic heart disease or myocardial infarction were relatively weak and not statistically significant after adjustment for potential risk factors
- Neither fish nor omega-3 PUFA dietary intake was associated with mortality from total stroke, its subtypes, or cardiac arrest
- For mortality from total cardiovascular disease, intakes of fish and omega-3 PUFA were associated with 18% to 19% lower risk

**Author Conclusion:**

We found an inverse association between fish and omega-3 PUFA dietary intakes and cardiovascular mortality, especially for heart failure in a large, nationwide, community-based Japanese cohort. This finding, taken together with those from prior studies, suggests a protective effect of fish intake on cardiovascular diseases.

***Reviewer Comments:***

- *Only half of the cohort had complete dietary information*
- *12.7 years of follow-up, but food frequency questionnaire only completed at baseline, and contained only 4 fish-related items out of 33 total items*

*Authors note the following limitations:*

- *For people who picked the highest categories of frequency, namely almost every day, the number of times fish was eaten could not be estimated; thus, the impact of misclassification may weaken the association*
- *23,339 subjects excluded due to incomplete dietary information; excluded subjects were older and more likely to be men than women compared with included subjects*
- *Possibility of residual confounding by other factors, healthy lifestyles, or socioeconomic status*

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***Research Design and Implementation Criteria Checklist: Primary Research***

| **Relevance Questions** | | |
|---|---|---|
| 1. | Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies) | N/A |
| 2. | Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about? | Yes |
| 3. | Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice? | Yes |
| 4. | Is the intervention or procedure feasible? (NA for some epidemiological studies) | N/A |

| **Validity Questions** | | |
|---|---|---|
| **1.** | **Was the research question clearly stated?** | Yes |
| 1.1. | Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified? | Yes |
| 1.2. | Was (were) the outcome(s) [dependent variable(s)] clearly indicated? | Yes |
| 1.3. | Were the target population and setting specified? | Yes |
| **2.** | **Was the selection of study subjects/patients free from bias?** | Yes |
| 2.1. | Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study? | Yes |

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|---|---|---|
| 2.2. | Were criteria applied equally to all study groups? | Yes |
| 2.3. | Were health, demographics, and other characteristics of subjects described? | Yes |
| 2.4. | Were the subjects/patients a representative sample of the relevant population? | Yes |
| **3.** | **Were study groups comparable?** | Yes |
| 3.1. | Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT) | N/A |
| 3.2. | Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline? | Yes |
| 3.3. | Were concurrent controls used? (Concurrent preferred over historical controls.) | N/A |
| 3.4. | If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis? | Yes |
| 3.5. | If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.) | N/A |
| 3.6. | If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")? | N/A |
| **4.** | **Was method of handling withdrawals described?** | Yes |
| 4.1. | Were follow-up methods described and the same for all groups? | Yes |
| 4.2. | Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.) | Yes |
| 4.3. | Were all enrolled subjects/patients (in the original sample) accounted for? | Yes |
| 4.4. | Were reasons for withdrawals similar across groups? | Yes |
| 4.5. | If diagnostic test, was decision to perform reference test not dependent on results of test under study? | N/A |
| **5.** | **Was blinding used to prevent introduction of bias?** | Yes |
| 5.1. | In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate? | N/A |

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|---|---|---|
| 5.2. | Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.) | Yes |
| 5.3. | In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded? | Yes |
| 5.4. | In case control study, was case definition explicit and case ascertainment not influenced by exposure status? | N/A |
| 5.5. | In diagnostic study, were test results blinded to patient history and other test results? | N/A |
| **6.** | **Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?** | Yes |
| 6.1. | In RCT or other intervention trial, were protocols described for all regimens studied? | N/A |
| 6.2. | In observational study, were interventions, study settings, and clinicians/provider described? | Yes |
| 6.3. | Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect? | Yes |
| 6.4. | Was the amount of exposure and, if relevant, subject/patient compliance measured? | N/A |
| 6.5. | Were co-interventions (e.g., ancillary treatments, other therapies) described? | N/A |
| 6.6. | Were extra or unplanned treatments described? | N/A |
| 6.7. | Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups? | N/A |
| 6.8. | In diagnostic study, were details of test administration and replication sufficient? | N/A |
| **7.** | **Were outcomes clearly defined and the measurements valid and reliable?** | Yes |
| 7.1. | Were primary and secondary endpoints described and relevant to the question? | Yes |
| 7.2. | Were nutrition measures appropriate to question and outcomes of concern? | Yes |
| 7.3. | Was the period of follow-up long enough for important outcome(s) to occur? | Yes |
| 7.4. | Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures? | Yes |
| 7.5. | Was the measurement of effect at an appropriate level of precision? | ??? |
| 7.6. | Were other factors accounted for (measured) that could affect outcomes? | Yes |
| 7.7. | Were the measurements conducted consistently across groups? | Yes |

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|---|---|---|---|
| **8.** | **Was the statistical analysis appropriate for the study design and type of outcome indicators?** | | Yes |
| | 8.1. | Were statistical analyses adequately described and the results reported appropriately? | Yes |
| | 8.2. | Were correct statistical tests used and assumptions of test not violated? | Yes |
| | 8.3. | Were statistics reported with levels of significance and/or confidence intervals? | Yes |
| | 8.4. | Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? | N/A |
| | 8.5. | Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? | Yes |
| | 8.6. | Was clinical significance as well as statistical significance reported? | Yes |
| | 8.7. | If negative findings, was a power calculation reported to address type 2 error? | N/A |
| **9.** | **Are conclusions supported by results with biases and limitations taken into consideration?** | | Yes |
| | 9.1. | Is there a discussion of findings? | Yes |
| | 9.2. | Are biases and study limitations identified and discussed? | Yes |
| **10.** | **Is bias due to study's funding or sponsorship unlikely?** | | Yes |
| | 10.1. | Were sources of funding and investigators' affiliations described? | Yes |
| | 10.2. | Was the study free from apparent conflict of interest? | Yes |